

King's Research Portal

DOI:

[10.1016/j.cortex.2017.05.009](https://doi.org/10.1016/j.cortex.2017.05.009)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Zahn, R. A., Green, S., Beaumont, H., Burns, A., Moll, J., Caine, D., Gerhard, A., Hoffman, P., Shaw, B., Grafman, J., & Lambon Ralph, M. A. (2017). Frontotemporal lobar degeneration and social behaviour: dissociation between the knowledge of its consequences and its conceptual meaning. *Cortex*, 93, 107+118. <https://doi.org/10.1016/j.cortex.2017.05.009>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Frontotemporal lobar degeneration and social behaviour: dissociation between the knowledge of its consequences and its conceptual meaning

Roland Zahn^{1,2,*}, Sophie Green², Helen Beaumont^{2,3}, Alistair Burns⁴, Jorge Moll⁵, Diana Caine^{2,6}, Alexander Gerhard^{4,7}, Paul Hoffman², Benjamin Shaw⁴, Jordan Grafman⁸, Matthew A. Lambon Ralph²

¹ *Institute of Psychiatry, Psychology & Neuroscience, Department of Psychological Medicine, King's College London, London, SE5 8AZ, UK*

² *Neuroscience and Aphasia Research Unit, Division of Neuroscience and Experimental Psychology, The University of Manchester, Manchester, UK*

³ *Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA*

⁴ *Division of Neuroscience and Experimental Psychology, The University of Manchester, Manchester, UK*

⁵ *Cognitive and Behavioral Neuroscience Unit, D'Or Institute for Research and Education (IDOR), Rio de Janeiro, RJ, Brazil*

⁶ *National Hospital for Neurology & Neurosurgery, Queen Square, London, UK.*

⁷ *Department of Nuclear Medicine and Geriatric Medicine, University Hospital Essen*

⁸ *Rehabilitation Institute of Chicago, Chicago, Illinois & Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, Illinois, USA*

This paper has been accepted for publication in Cortex (all rights reserved)

** To whom correspondence should be addressed:*

Dr. Roland Zahn (see address above)

E-mail: roland.zahn@kcl.ac.uk

Phone: 0044-(0)20 7848 0348

Fax: 0044-(0)20 7848 0298

This is a pre-print of an article to appear in CORTEX (all rights reserved)

Key words: Brodmann Area 10, Social Behaviour, Impulsivity, Disinhibition, Frontal Lobe

Highlights

- Employs the first semantic test of knowledge of consequences of social behaviour
- Double dissociations for long-term vs. short-term consequences and social concepts
- Evidence for neuroanatomical separation of these social knowledge components
- Relative frontopolar atrophy correlates with impairment on long-term consequences
- Relative anterior temporal atrophy correlates with impairment on social concepts

Abstract

Inappropriate social behaviour is an early symptom of frontotemporal lobar degeneration (FTLD) in both behavioural variant frontotemporal dementia (bvFTD) and semantic dementia (SD) subtypes. Knowledge of social behaviour is essential for appropriate social conduct. The superior anterior temporal lobe (ATL) has been identified as one key neural component for the *conceptual knowledge* of social behaviour, but it is unknown whether this is dissociable from knowledge of the *consequences* of social behaviour. Here, we used a newly-developed test of knowledge about long-term and short-term consequences of social behaviour to investigate its impairment in patients with FTLD relative to a previously-developed test of social conceptual knowledge. We included 19 healthy elderly control participants and 19 consecutive patients with features of bvFTD or SD and defined dissociations as performance differences between tasks for each patient (Bonferroni-corrected $p < .05$). Knowledge of long-term consequences was selectively impaired relative to short-term consequences in five patients and the reverse dissociation occurred in one patient. Six patients showed a selective impairment of social concepts relative to long-term consequences with the reverse dissociation occurring in one patient. These results corroborate the hypothesis that knowledge of long-term consequences of social behaviour is dissociable from knowledge of short-term consequences, as well as of social conceptual knowledge. Confirming our hypothesis, we found that patients with more marked grey matter volume loss in frontopolar relative to right superior ATL regions of interest exhibited poorer knowledge of the long-term consequences of social behaviour relative to the knowledge of its conceptual meaning and vice versa ($n=15$). These findings support the hypothesis that frontopolar and ATL regions represent distinct aspects of social knowledge. This suggests that rather than being unable to suppress urges to behave inappropriately, FTLD patients often lose the knowledge of what appropriate social behaviour is and can therefore not be expected to behave accordingly.

Introduction

Social knowledge has been defined as knowledge of one's own and other people's minds (Adolphs, 2009). Because "mind" or "mental states" are hard to break down neuropsychologically, we prefer defining social knowledge as denoting non-episodic (i.e. semantic) knowledge of social sensory properties and social behaviour (i.e. functions,(Zahn et al., 2015)). Socially appropriate behaviour requires knowledge of adequate social actions within a given short-term sequential context (e.g. "to appropriately touch a romantic partner after a romantic date" but not "the waiter/waitress after dinner in a restaurant" (Wood and Grafman, 2003)). Socially appropriate behaviour also requires anticipating possible long-term consequences (e.g. "being unemployed with a criminal record for sexual harassment" as a consequence of e.g. "inappropriate touching"), but also knowledge of the abstract conceptual quality of a given social action within a given context (e.g. enabling us to flexibly interpret "not being greeted by a colleague who is passing by in a corridor at work" as a sign of "disrespect", "impoliteness", "shyness" or "absent-mindedness" (Zahn et al., 2009a)).

Using fMRI and transcranial magnetic stimulation (TMS) methods, we have demonstrated that this abstract conceptual social knowledge, which is independent of the context of actions (Zahn et al., 2009b) and emotions (Zahn et al., 2007; Zahn et al., 2009b), is represented in the superior anterior temporal lobe (ATL:(Pobric et al., 2016)). FMRI studies have shown that the ATLs, especially within their superior sectors (Skipper et al., 2011; Zahn et al., 2007), are selectively more activated when considering social concepts than they are for non-social concepts (Ross and Olson, 2010; Simmons et al., 2009; Skipper et al., 2011; Zahn et al., 2007), whereas the ventral ATL is equally engaged for social and non-social concepts (Binney et al., 2016). Furthermore, right superior ATL activation increased with the richness of detail with which social

concepts describe social behaviour (Zahn et al., 2007). This is in keeping with the role of the ATLs in representing coherent conceptual knowledge (Lambon Ralph and Patterson, 2008; Patterson et al., 2007). Frontotemporal lobar degeneration (FTLD) patients with hypometabolism of the right ATL showed selective impairments on social relative to non-social concepts (Zahn et al., 2009a). Furthermore, two rare cases with selective right and left ATL atrophy respectively showed selective impairments on social vs. non-social concepts in the right ATL and an impairment of both types of concepts in the left ATL case (Pobric et al., 2016). These results were in keeping with repetitive TMS of the right and left superior ATL, showing a selective slowing of social relative to non-social concepts in the right superior ATL, as well as a slowing of social and non-social conceptual task responses relative to a non-semantic control condition in the left superior ATL (Pobric et al., 2016). These findings were in keeping with a larger body of evidence on graded hemispheric and regional specialisation within the anterior temporal lobes for different conceptual content (Rice et al., 2015a; Rice et al., 2015b).

Less is known about the representation of sequential social knowledge. Non-social sequential knowledge was associated with lateral frontal neurodegeneration by showing impairments in the hierarchical organisation of non-social scripts as measured by event ordering tasks (Farag et al., 2010). The structured event complex theory (Wood and Grafman, 2003) posited that the prefrontal cortex is a long-term memory store for event/action sequences (also referred to as “scripts”) with the frontopolar cortex (BA10) representing the most sequentially complex information (Moll et al., 2005). The specific association of the medial frontopolar cortex with complex sequential representations has been corroborated in fMRI studies in healthy control participants by directly modelling the number of events (Krueger et al., 2009) entailed in daily life activities (e.g. going shopping) and their frequency of occurrence (Krueger et al., 2007a), as well as participants’ sequential rule knowledge (Wood et al., 2005a). Patients with frontal lesions or

neurodegeneration which included the frontopolar cortex were shown to perform poorly on tasks that require sequencing daily life activities (i.e. ordering component events into a sequential order, (Krueger et al., 2007b; Sirigu et al., 1996)) and structuring events for real-world planning (Goel et al., 1997), whilst performing normally on making superordinate-subordinate judgements about daily life event themes and component events once executive demands were controlled for (Wood et al., 2005b). Focal lesions of the ventromedial and medial frontopolar cortex rather than the dorsolateral frontal cortex were also associated with a reduced tendency to look into the long-term future (Fellows and Farah, 2005). Medial frontopolar neurodegeneration was further associated with selective impairments of complex socio-moral emotions such as guilt which require representing the long-term consequences of social behaviour (Moll et al., 2011) and this concurred with fMRI evidence on medial frontopolar activation for guilt (Basile et al., 2011; Kedia et al., 2008; Moll et al., 2007; Morey et al., 2012; Takahashi et al., 2004; Zahn et al., 2009b) relative to other complex negative emotions. Socially and emotionally-relevant event sequences, particularly those of personal relevance (Forbes and Grafman, 2010), were hypothesized to be represented in ventral frontal cortical areas (Moll et al., 2005; Wood and Grafman, 2003). To our knowledge, however, all previous neuropsychological investigations of sequential knowledge have used tasks that required active sequencing and it is thus impossible to clearly disentangle their requirement for executing a sequencing task from their requirement of knowing about the correct sequence.

FTLD is a heterogeneous disorder including clinical syndromes of Semantic Dementia (SD) and behavioural variant frontotemporal dementia (bvFTD) predominantly affecting anterior temporal and frontal, including frontopolar, cortices. Despite their anatomical heterogeneity, both variants display consistent and early inappropriate social behaviour (Bozeat et al., 2000a; Liu et al., 2004; McKhann et al., 2001; Snowden et al., 2001). The study of the cognitive neuropsychology of social behaviour in FTLD is therefore a crucial test of whether social

knowledge is important for appropriate social behaviour. One possibility is that the atrophy to the frontal lobes in FTLN (Miller et al., 1991; Miller et al., 1997; Neary et al., 1998; Neary et al., 1993), is largely responsible for inappropriate social behaviour, as the posterior orbitofrontal cortex is regularly affected in SD as well (Liu et al., 2004; Mummery et al., 2000; Rosen et al., 2002). This is contradicted by the findings that ATL (Zamboni et al., 2008) and ventromedial frontal cortex (including parts of the frontopolar cortex) are both independently associated with inappropriate social behaviour in FTLN (Liu et al., 2004). Thus, whilst it is largely undisputed that both frontal and ATL regions contribute to inappropriate social behaviour in FTLN (Sollberger et al., 2009), it is still unclear what their respective functional contributions are. One popular model derived from non-human animal conditioning experiments postulates disinhibited frontal suppression of subcortically-mediated behavioural urges (Brutkowski, 1965) resulting in “disinhibited” behaviour in frontal lesion patients. Underlying, the frontal suppression model is the assumption that frontal damage does not impair knowledge of the appropriateness of one’s urges, only the ability to control them. There is contradictory evidence, however, on whether social knowledge is intact in patients with bvFTD who regularly demonstrate such damage (Grossman et al., 2010; Mendez, 2010; Mendez et al., 2005a; Mendez et al., 2005b). Furthermore, there has been no investigation of whether different patients with FTLN exhibit dissociable deficits between different forms of social knowledge, which could underpin shared social behavioural changes in patients with non-overlapping patterns of neurodegeneration.

So far, there has been no direct comparison of social sequential and conceptual knowledge in patients due to the lack of semantic tasks that probe sequential social knowledge. We designed such a novel task to probe knowledge of short- and long-term consequences of social behaviour and used this alongside our previously developed Social Concept Discrimination Task (Zahn et al., 2009a) and a control task, the Visual Discrimination Task to investigate whether there are

dissociable deficits in these knowledge forms that would support the hypothesis of their neuroanatomical separation (Moll et al., 2005). Specifically, we hypothesised that knowledge of social behaviour can be separated into three components which are neuroanatomically distinct and should therefore give rise to double dissociations at the single patient level (Shallice, 1990), such that we expected to find patients with 1) selective impairments on knowledge of long- vs. short-term consequences, 2) long-term vs. social conceptual knowledge and the respective reverse dissociations. We further hypothesised that 3) patients with relatively reduced grey matter volumes in their frontopolar cortices vs. right superior ATL would show poorer knowledge of long-term consequences relative to social conceptual knowledge and vice versa. Our approach is based on the cognitive neuropsychology method and the notion that impairments on neuropsychological tasks are due to multiple cognitive components, which is why we focus on the performance difference of a patient between closely matched task conditions that differ on a cognitive component to be probed (Shallice, 1990). These so called “dissociations” in performance point to a difference in performance between conditions due to differential impairment of the cognitive component varied between the conditions. Recent statistical approaches have been developed and are well established to formally probe single case dissociations (Crawford and Garthwaite, 2005).

1. Material and Methods

1.1. Patients and controls

Patients were referred from old age psychiatry community teams, the Cerebral Function Unit (AG) at Salford Royal Hospital or seen in the South Manchester University Hospital Memory Clinic (RZ, AB). Four semantic dementia patients were assessed as part of a study led by MALR and described elsewhere (Hoffman et al., 2012). Patients were referred to MALR for study

participation from the Research Institute for Care of the Elderly (RICE) institute in Bath after previously receiving a diagnosis of SD from a consultant neurologist (Prof. Roy Jones). Patients provided written informed consent for participation in accordance with a Multicentre Research Ethics Committee approved protocol and a South Manchester NHS Research Ethics Committee approved protocol which also allowed for carer assent-based inclusion if patients agreed to the study but lacked the capacity to consent. Participants were compensated for their time and travel.

All Manchester patients were clinically assessed by a senior old age psychiatrist (RZ) or senior neuropsychologist (MALR) and underwent extensive neuropsychological test examination as well as MRI in most cases or CT. General inclusion criteria for this study were strong right-handedness and English as first language. Diagnosis of FTLD (including those with features of bvFTD, or of SD, as well as mixed presentations) was based on clinical, neuropsychological criteria as well as visual inspection of MRI/CT scans and followed established consensus criteria [FTLD: Lund-Manchester criteria (Neary et al., 1998)] shown to have excellent neuropathological validity (Snowden et al., 2011) and which, contrary to more recent consensus criteria that strictly separate progressive aphasia and behavioural variants and were primarily developed by cognitive neurologists (Gorno-Tempini et al., 2011; Rascovsky et al., 2011), allow for mixed subtype presentations, which are common in our experience when detailed neuropsychiatric assessments are carried out.

SD patients had a history of at least two years of prominent impairment of communication without further clinically relevant symptoms. SD patients had fluent speech with comprehension and naming impairments as their lead symptom. As stipulated by the Lund-Manchester criteria (Neary et al., 1998), the lead symptoms in bvFTD patients were progressive dysexecutive or behavioural abnormalities with an early loss of insight as noted by caregivers. Early amnesia and

visuo-spatial deficits were absent in the history of all FTLD patients. All FTLD patients showed abnormalities within frontotemporal areas upon visual inspection of MRI or CT scans.

24 patients with a suspected clinical diagnosis of FTLD were consecutively enrolled. 5 FTLD patients had to be excluded prior to the statistical analysis (n=1 who struggled to complete the experimental tasks, n=1 whose family withdrew assent, n=3 where the assessment resulted in a different diagnosis: 1 affective disorder, 1 Alzheimer's dementia, 1 phenocopy syndrome) leading to a final FTLD sample of n=19 (8 male, age: mean=67.3±8.3 years, education: mean=12.3±3 years; ± refers to standard-deviation throughout the text). FTLD patients had been clinically classified into SD (n=5), SD with features of bvFTD (n=2), bvFTD (n=6), bvFTD with features of SD (n=4) and mixed primary progressive aphasia (logopenic & SD) with secondary features of bvFTD (n=1), as well as mixed primary progressive aphasia (nonfluent & SD) with secondary features of bvFTD (n=1). The final sample of n=19 control participants (10 male) was younger (age: mean=60.7±9.1; years $t=-2.3$, $p=.03$) and showed a trend towards being more highly educated (education: mean=14.2±3.2 years; $t=1.9$, $p=.06$), which is why education- and age-effects were investigated as potential confounders in all analyses comparing FTLD vs. control groups. Gender was matched between groups (Contingency Coefficient=.11, $p=.52$). 15 participants from each group were included in the MRI part of the study with gender (Contingency Coefficient=.13, $p=.46$) and education ($t=1.5$, $p=.14$) matched, but a trend towards healthy control participants being younger ($t=-1.8$, $p=.08$). 4 patients were not able to undergo research MRI, because they were assessed in Bath.

All 25 healthy volunteers had no history of psychiatric, neurological or relevant medical disorders as assessed by a clinical history with specific probe questions (one had been excluded before on screening because of a history of hypothyroidism and one because of epilepsy). Of the 25 control participants, three had to be excluded because of abnormal results on the

Addenbrooke's Cognitive Examination-R, and three were excluded because of MRI abnormalities (excessive atrophy: 1, marked cerebrovascular small vessel disease: 1, arachnoid cyst: 1) resulting in a final sample of n=19 for the neuropsychological part of the study, 4 were excluded from the MRI part of the study because of MRI contraindications leading to a final sample of n=15 for the MRI study.

1.2. Neuropsychological Test Examination

Core background neuropsychological tests included the Addenbrooke's Cognitive Examination (ACE-R, version A, 2005, (Mioshi et al., 2006)), and the Cambridge 64 item Semantic Battery including Naming, and Word-to-Picture Matching (Bozeat et al., 2000b).

Participants completed the Visual Discrimination Task, Social Concept Discrimination Task, and the Consequences of Social Action Task without prior training as self-paced tasks using the presentation software E-Prime, <http://www.pstnet.com/eprime.cfm>, version 1.1. They were designed in analogy to the Pyramids and Palm Trees Test (Howard and Patterson, 1992) in which a probe item was presented at the top of a screen and participants had to decide which of two stimuli at the bottom was more related to the probe. For all tasks, patients and control participants were asked to point to their chosen response on the screen and the experimenter operated the keys to register the response. The stimuli were always presented in a random order and the position of the target and distracter was counterbalanced across trials. The experimenter read the probe word and pointed to each of the stimuli at the bottom in turn, starting with the one on the left, and then the one on the right. Stimuli were presented in a white font on a black background.

The Visual Discrimination Task is a non-verbal control task (Figure 1c), created by SG and was administered to control for the task demands of the Social Concept Discrimination Task and

the Consequences of Social Action Task. It is comprised of 2D line drawings of black and white figures that are of no resemblance to real objects (Gauthier et al., 2003); stimulus images courtesy of Michael J. Tarr, Center for the Neural Basis of Cognition and Department of Psychology, Carnegie Mellon University, <http://www.tarrlab.org/>. The original line drawings were slightly modified to produce 24 triads whereby there is a probe figure, a target figure that is similar (not identical) to the probe (only one difference in line arrangements between the two) and a distracter figure that is different to both (three differences in lines between distracter and probe, and between distracter and target). A target that was similar rather than the same as the probe was used so that the task reflected the demands of the Social Concept Discrimination Task. The participant was asked to point to the “figure which is most related to the figure at the top”.

For the Social Concept Discrimination Task (previously described by Zahn et al., (2009a), Figure 1a) target (e.g. “courage”) and distracter (e.g. “controlled”) concepts were chosen from the same category as the probe concepts (e.g. social concept probe: “adventurous”; animal function concept probe: “trainable”, target: “ridden”, distracter: “bites”) and had been used in our previous fMRI studies (Zahn et al., 2007; Zahn et al., 2009b). Participants were presented with six training triads followed by 73 stimulus items presented in a random order (25 positive social concept triads, 24 negative social concept triads, 24 animal function concept triads). The full description of matching of relevant psycholinguistic variables and data from n=30 controls, n=29 FTD and n=18 corticobasal degeneration patients are available in Zahn et al. (2009a). Stimulus items were previously established to have 80% response agreement in a normative study (Zahn et al., 2009a). Participants were asked to point to the word which was most related to the word at the top (experimenter points to the probe at the top of the screen).

The Consequences of Social Action Task, created by SG, was then administered (for details of the design of the task, please see Supplementary Materials and Figure 1b). This task was

comprised of 60 triads with a probe social behaviour, and two alternative consequences, a target consequence that was more related to the behaviour, and a less related distracter consequence (30 long-term consequences: 15 positive and 15 negative, 30 short-term consequences: 15 positive, 15 negative). In any one trial, both of the consequences (target and distracter) were either long-term or short-term. Participants were asked to point to the “consequence which was most related to the social behaviour”, and the experimenter pointed to the statements whilst explaining the instructions. Example of short-term consequences (Probe: “You punish an employee at work”, Target: “They verbally attack you”, Distracter: “They violently attack you”). Example of long-term consequences (Probe: “You ignore your employers’ requests at work”, Target: “Your standard of living decreases”, Distracter: “You are violently attacked”). All experimental tasks are available at: <http://www.translational-cognitive-neuroscience.org/start/test-materials> or from the authors.

1.3. Statistical analysis of experimental tasks

We tested for strong dissociations between two impaired scores on two task conditions (% correct), using a modified paired samples t-test and the Revised Standard Difference Test (RSDT) of Crawford & Garthwaite (2005) implemented in the software created by the authors (<http://www.abdn.ac.uk/~psy086/dept/SingleCaseMethodology.htm>). The RSDT has been shown to adequately control for error rates even in small samples (Crawford and Garthwaite, 2005) and is a well-established method for probing single case dissociations. The mean and standard deviation for each test/condition from the control group was entered, the correlation between scores on these tests conditions/tests, together with the sample size of the control group and the patients scores on the two tests. Dissociations were considered at an individual threshold of $p < .0026$ (corresponding to an approximate Bonferroni-corrected $p < .05$ across 19 single patient cases) for long-term vs. short-term consequences and social concept vs. long-term consequences conditions.

The only potential variables to be controlled for in patients with selective impairments on long-term vs. short-term consequences that differed between the conditions were target median familiarity and median likelihood (lower in the long-term consequences condition). This was achieved by computing individual binary logistic regression models (SPSS 15.0) for each subject in the FTL group in which a significant dissociation between long-term and short-term consequences conditions had occurred. Familiarity and likelihood per stimulus were predictor covariates in separate models and correct/incorrect response the categorical outcome in both models (no constant modelled).

1.4. Image acquisition

All images were acquired with a Philips Achieva 3T scanner using an 8-channel head-coil. The T1-weighted sequence was a high-resolution 3D MPRAGE, inversion time 1150ms, 256x164 matrix, 128 slices, voxel size=1mm³, TE=3.8ms, TR 9.4ms, flip angle 80. T2-weighted images were acquired using a turbospin-echo sequence with SENSE factor 2. Matrix size was 512x408, 44 slices, voxel size 0.26mm x 0.26mm x 3.30mm, TE 80ms, TR3s, flip angle 900. This sequence was used to exclude participants with marked cerebrovascular, or other non-degenerative changes.

1.5. Image analysis

Imaging data were analyzed using statistical parametric mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8>). Images were inspected for artefacts (motion, high level of inhomogeneities) before and after normalization. T1-images were normalized and segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the new features of the VBM8 toolbox, version 359 (<http://dbm.neuro.uni-jena.de/vbm>): segmentation without tissue priors, labelling voxels according to their tissue types using partial volume estimation (PVE), de-noising with non-local means filter and integration of DARTEL

normalization (Ashburner, 2007). After pre-processing, images (1.5x1.5x1.5 mm³ voxel size) were smoothed with a Gaussian kernel of FWHM = 12 mm. The “non-linear modulation only” option (i.e. with no affine component) was selected to create volumetric GM and WM partitions. This option is recommended to obtain relative volume after correcting for differences in brain size and replaces earlier methods of using total intracranial volume or total GM+WM (<http://dbm.neuro.uni-jena.de/vbm/segmentation/modulation/>) as nuisance covariates. Thorough clean-up was selected as recommended for atrophied brains. A 0.2 absolute threshold masking was used to select voxels for the subsequent statistical analysis. We extracted the voxel grey matter volumes in our two a priori regions of interest (ROIs): frontopolar cortex (Brodmann Area [BA] 10; MNI: -2, 66, 20) and right superior ATL (MNI: 58, 0, -12) and our two control regions: subgenual cingulate cortex (MNI: -4, 23, -5) and left superior ATL (mirror region of the right) using 6 mm radius spheres around centre coordinates from our previous paper revealing functional connectivity changes in this network in major depressive disorder which is associated with overgeneralized interpretations of social behaviour (Green et al., 2012) using the Marsbar toolbox (Brett et al., 2002). The subgenual cingulate was chosen as a control region because it is part of a posterior ventromedial frontal region that has been associated with impaired judgments of acceptability of social rule violations in patients with frontotemporal lobar degeneration (Grossman et al., 2010) and is functionally connected with our right superior ATL region whilst evaluating social behaviour (Green et al., 2010).

2. Results

2.1 Group comparisons

Group comparisons of our patients with healthy control participants (Table 1) showed that general semantic and social conceptual impairments were consistently observed in our FTLD group, whereas more variability existed in performance on the sequential social knowledge task. As expected, almost all patients performed normally on the visual discrimination task.

2.2 Dissociations at the individual level

As predicted, we observed double dissociations between our three social knowledge task conditions of interest. One patient exhibited a selective impairment on long-term consequences vs. social concepts (FTD_7). He was also among five patients displaying selective impairments on long-term consequences relative to short-term consequences (Figure 2; FTD_07, FTD_09, FTD_13, FTD_16, FTD_18). Another patient displayed a selective impairment on short-term vs. long-term consequences (SD_11). In contrast, six patients showed selective impairments on social concepts relative to long-term consequences (FTD_3, FTD_10, FTD_21, SD_11, SD_12, SD_13).

All five patients with selective impairments on long-term vs. short-term consequences were further examined using individual logistic regression models to determine the potential confounding influence of lower target consequence likelihood and familiarity in the long-term relative to the short-term consequences condition. Target consequence familiarity had no effect on task performance in any patient ($p > .07$, Wald < 3.4), and likelihood significantly affected performance only in one case such that target consequences with higher rated likelihood were more often correctly selected (FTD_16: $B = .036$, Standard error = .018, Wald = 3.87, $df = 1$, $p = .05$). The condition effects on performance (long-term $<$ short-term consequences) disappeared when correcting for effects of likelihood as a covariate in this case.

2.3 Neuroanatomy of performance differences between long-term consequences and social concepts

There were no significant effects of age or education on the differences in performance between long-term consequences relative to social concepts (Control group, $n=19$: age: $\rho=.10$, $p=.68$, education: $\rho=-.28$, $p=.24$; FTL group, $n=19$, age: $\rho=.06$, $p=.79$, education: $\rho=-.24$, $p=.33$) or relative to short-term consequences (Control group, $n=19$: age: $\rho=.27$, $p=.27$, education: $\rho=-.13$, $p=.59$; FTL group, $n=19$, age: $\rho=.19$, $p=.43$, education: $\rho=.05$, $p=.83$) in either group.

As hypothesised, difference scores for performance on the long-term consequences vs. social concept task conditions were positively associated with difference scores in frontopolar cortex (i.e. BA10) vs. right superior ATL grey matter volumes in the FTL group ($F[14,1]=5.50$, $p=.04$, $R^2=.30$, Figure 3). Lower frontopolar relative to ATL volume was associated with poorer performance on long-term consequences relative to social concepts and vice versa. This was also the case when correcting for age ($t=2.35$, partial $\beta=.56$, $p=.04$ for the effect of interest with no effect of age: $t=-.65$, partial $\beta=-.12$, $p=.53$). The control group showed no such relationship between neuropsychological and brain region difference scores ($F[14,1]=.001$, $p=.97$, $R^2<.0001$). As expected there was also no association when using a difference score of volume in our control regions subgenual cingulate – left superior ATL ($F[14,1]=.60$, $p=.45$, $R^2=.04$). In a supporting analysis we also modelled the frontopolar vs. right superior ATL difference score together with the control region difference score and demonstrated that the association of our regions of interest with our neuropsychological measure of interest remains significant even when directly adjusting for the effects of the control regions (partial $\eta^2=.41$, $t=2.9$, $p=.01$). There was no association between our neuropsychological measure of interest and grey matter volumes when using a difference score of volume in the frontopolar cortex – left superior ATL ($F[14,1]=.63$, $p=.44$) showing that no similar relationship exists for the left superior ATL.

All values on the difference scores used were within 2.5 standard deviations of the respective group mean suggesting that outlying values were unlikely to influence the results. This was further corroborated by using additional non-parametric (i.e. rank- rather than normal distribution-based) statistics. This confirmed the positive correlation of long-term consequences vs. social concept task difference scores with difference scores in frontopolar cortex vs. right superior ATL grey matter volumes in the FTL group (Spearman $\rho=.51$, $p=.05$).

3. Discussion

We confirmed our hypotheses that knowledge of long-term consequences of social behaviour can be dissociated from both the knowledge of short-term consequences and social concepts. This finding indicates at least partly distinct neuroanatomical representations. We further confirmed our hypothesis that frontopolar cortical relative to right superior ATL grey matter volume loss is associated with poorer performance on long-term consequences relative to social concepts and vice versa. This provides the first direct association of neuropsychological probes of sequential knowledge with frontopolar cortical volumes.

These findings are in keeping with the hypothesis that semantic (i.e. non-episodic) knowledge of social behaviour can be divided into a conceptual component within the ATL and a non-conceptual component in the frontal cortex (Zahn et al., 2011). The high frequency of impairments on knowledge of long-term consequences in our FTL group is also in keeping with findings from glucose positron emission tomography (PET) showing that ventromedial frontopolar areas are most consistently impaired in bvFTD (Salmon et al., 2003).

Our finding of impairments of long-term sequential social knowledge in about half of our FTL patients including patients with bvFTD contradicts the conclusions drawn from previous

studies assessing social knowledge in bvFTD with clinical interviews. Mendez et al. (2005b) did not find social knowledge in their bvFTD sample to be impaired and stated that all 16 patients had knowledge of the outcomes of their behaviours and “could describe the potential consequences of their actions, but 12 did not feel ‘very concerned’ about them. Nine patients minimized the impact of their behavior, but none gave more extensive rationalization”. Another study by Mendez and Shapira (2009) probed FTD patients’ social knowledge by asking them how right or wrong certain actions are (e.g. “take the last seat on a crowded bus”), and revealed no impairments in knowledge of these social conventions. A possible explanation for the discrepancy with our finding is that the knowledge of behaviour probed in these studies did not require consideration of long-term consequences because they were overlearned social ‘rules’ or may not result in long-term consequences per se.

Interestingly, in contrast to Mendez and Shapira (2009), Grossman et al., (2010) demonstrated that FTLT patients more readily endorse statements asking for the social acceptability of social violations than healthy control participants, therefore demonstrating impaired social knowledge. The items used in this study included the violation of a social convention (e.g. “running a red light”) as well as additional contextual detail, (e.g. “You run a red light at 2am in the morning”) and so may have more readily demanded sequential knowledge due to the variability of different consequences that could occur. For example, whilst running a red light is an over-learned driving violation, the consequence that may arise is very different if it occurs at 2 am in the morning (e.g. “no one else will be around” \Rightarrow “I might not get caught” \Rightarrow “I won’t cause an accident”), rather than in the middle of the day (e.g. “lots of people around” \Rightarrow “someone could get hurt” \Rightarrow “I might get caught” \Rightarrow “I could get into trouble with the law”). This could explain differences between the results of (Mendez and Shapira, 2009) and Grossman et al., (2010), where the authors hypothesised that the impairments of FTLT patients could arise from

their inability to anticipate the negative consequences of their behaviour; a hypothesis which is directly supported by our results.

Our results also need discussing in the context of studies in patients with non-neurodegenerative ventral frontal lobe lesions which have consistently demonstrated that the integrity of this region is critical for normal moral development and social conduct (Anderson et al., 2006; Anderson et al., 1999; Blair and Cipolotti, 2000; Eslinger and Damasio, 1985). EVR developed impairments in social behaviour as a result of removal of a meningioma in the ventral frontal lobes (Eslinger and Damasio, 1985; Saver and Damasio, 1991). In contrast to our findings, however, his performance on a task probing his knowledge of the consequences of social behaviours was intact (Saver and Damasio, 1991). One possible explanation for this discrepancy is that the employed test may have relied more heavily on probing short- rather than long-term consequences and may have also relied on overlearned associative knowledge which may be more redundantly stored. Future studies, comparing performance of patients with ventral and frontopolar brain lesions on our test as well as other tests of social knowledge are required to fully account for the discrepancies.

The relationship between clinical diagnosis and profile of social knowledge impairment was examined in a supporting analysis (Supplementary Table 4) which was in keeping with our main analysis such that patients with suspected primary involvement of the ATLs (i.e. those with primary SD or primary atrophy of the ATLs) performed more poorly on social concepts relative to long-term consequences and showed lower ATL relative to frontopolar volume. As expected, the reverse pattern arose for patients whose neurodegeneration was suspected to have started outside the ATL on the basis of their clinical presentation and/or neuroimaging inspection (primary bvFTD or no ATL atrophy). This analysis was not the main focus of our paper, because of the uneven distribution of clinical groups with only a small number of non-ATL patients. The higher

proportion of ATL patients was also reflected in the overall pattern of grey matter volume loss which consistently involved anterior temporal, but not frontopolar brain regions (Supplementary Figure 3 & Supplementary Table 5).

In further supporting analyses (Supplementary Table 2 & 3), we showed that performance on general semantic tests and the verbal subtests of the ACE-R in our patients was associated with performance on social concepts as we would have predicted, but interestingly to similar degrees also between general semantic tests and short-term consequences, but not the long-term consequences task. We know that general semantic abilities are required for all tasks, but it appears that differences in performance between patients on long-term consequences were driven by additional requirements not captured by standard semantic tests. In contrast, part of the differences in performance on short-term consequences could have been driven by general semantic abilities. Alternatively, general semantic abilities could have been associated with performance on short-term consequences, because patients with semantic dementia were shown to exhibit neurodegeneration in posterior ventral frontal areas (Liu et al., 2004; Mummery et al., 2000; Rosen et al., 2002) hypothesised to represent short-term (i.e. less complex) social consequences/outcomes (Moll et al., 2005; Wood and Grafman, 2003). This highlights the importance of restricting one's interpretation to dissociations between tasks rather than overall task performance as we have done throughout this paper.

On a more cautionary note, we did not have the opportunity to gather glucose PET data in our patients, known to be more sensitive to early neurodegenerative changes, especially in the frontal cortex in FTLN (Salmon et al., 2003) compared to T1-weighted structural MRI (Hodges, 2001). Future replication of our association of relatively pronounced frontopolar damage with relatively pronounced impairments on long-term consequences are therefore needed using a more sensitive neuroimaging probe of frontal integrity. Ideally, future studies would aim for a larger subgroup of patients with frontopolar neurodegeneration who do not exhibit ATL pathology and a

larger overall sample size to provide more reliable estimates of effect size. This will be challenging, however, because at a group level, patients with bvFTD also demonstrated ATL involvement (Salmon et al., 2003), but prospective studies in families of patients with FTLT may provide such an opportunity. The battery of experimental tests to probe social knowledge in the current study is well suited for further investigations, because the overall task demands were similar between the different conditions (two forced choices matched to a probe) and the verbal working memory load between short-term and long-term consequences task conditions was matched.

4. Conclusions

Taken together, our data support the hypothesis that knowledge of long-term consequences of social behaviour is dissociable from knowledge of its short-term consequences, as well as of social concepts. These cognitive neuropsychological dissociations support separable neuroanatomical representations of these different components of social knowledge. Furthermore, we found support for the hypothesis that frontopolar cortical volume loss is selectively associated with impoverished knowledge of the long-term consequences of social behaviour, whilst confirming our previously established association of disrupted social conceptual knowledge with right superior ATL neurodegeneration. Future studies are needed to confirm the proposed role of the frontopolar cortex in representing long-term consequences of social behaviour. Our results suggest that rather than being unable to suppress urges to behave inappropriately, FTLN patients often lose the knowledge of what appropriate social behaviour is and can therefore not be expected to behave accordingly. Patients losing knowledge of the long-term consequences of behaviour can be expected to act seemingly more “impulsively”, without having to postulate a deficit in their ability to suppress urges and such claims should be used more cautiously.

Acknowledgements

This study was supported by a Stepping Stones Fellowship award to RZ (Faculty of Medical & Human Sciences, The University of Manchester). RZ was in part supported by MRC clinician scientist fellowship (G0902304). JM was supported by the D’Or Institute for Research and Education, Rio de Janeiro, Brazil. We are grateful to Prof. Roy Jones, Dr. Joy Ratcliffe and Dr. Andrew Larner for referring patients into our study and to patients and carers for their

participation. SG was supported by an MRC PhD studentship. MALR was supported by an MRC programme grant (MR/J004146/1).

References

- Adolphs, R. The Social Brain: Neural Basis of Social Knowledge. *Annual Review of Psychology*, 2009. 60: 693-716.
- Anderson, S.W., Barrash, J., Bechara, A., Tranel, D. Impairments of emotion and real-world complex behavior following childhood- or adult-onset damage to ventromedial prefrontal cortex. *J Int Neuropsych Soc*, 2006. 12 (2): 224-235.
- Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., Damasio, A.R. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature Neuroscience*, 1999. 2 (11): 1032-1037.
- Ashburner, J. A fast diffeomorphic image registration algorithm. *Neuroimage*, 2007. 38 (1): 95-113.
- Basile, B., Mancini, F., Macaluso, E., Caltagirone, C., Frackowiak, R.S.J., Bozzali, M. Deontological and Altruistic Guilt: Evidence for Distinct Neurobiological Substrates. *Human Brain Mapping*, 2011. 32 (2): 229-239.
- Binney, R.J., Hoffman, P., Lambon Ralph, M.A. Mapping the Multiple Graded Contributions of the Anterior Temporal Lobe Representational Hub to Abstract and Social Concepts: Evidence from Distortion-corrected fMRI. *Cereb Cortex*, 2016.
- Blair, R.J.R., Cipolotti, L. Impaired social response reversal - A case of 'acquired sociopathy'. *Brain*, 2000. 123: 1122-1141.
- Bozeat, S., Gregory, C.A., Lambon Ralph, M.A., Hodges, J.R. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry*, 2000a. 69 (2): 178-186.
- Bozeat, S., Lambon Ralph, M.A., Patterson, K., Garrard, P., Hodges, J.R. Non-verbal semantic impairment in semantic dementia. *Neuropsychologia*, 2000b. 38 (9): 1207-1215.
- Brett, M., Jean-Luc Anton, J.L., Valabregue, R., Poline, J.B. Region of interest analysis using an SPM toolbox. *8th International Conference on Functional Mapping of the Human Brain*: Sendai, Japan, 2002.
- Brutkowski, S. Functions of prefrontal cortex in animals. *Physiol Rev*, 1965. 45 (4): 721-746.
- Crawford, J.R., Garthwaite, P.H. Testing for suspected impairments and dissociations in single-case studies in neuropsychology: Evaluation of alternatives using Monte Carlo simulations and revised tests for dissociations. *Neuropsychology*, 2005. 11 (3): 97-104.
- Eslinger, P.J., Damasio, A.R. Severe Disturbance of Higher Cognition after Bilateral Frontal-Lobe Ablation - Patient EVR. *Neurology*, 1985. 35 (12): 1731-1741.
- Frag, C., Troiani, V., Bonner, M., Powers, C., Avants, B., Gee, J., Grossman, M. Hierarchical organization of scripts: converging evidence from FMRI and frontotemporal degeneration. *Cereb Cortex*, 2010. 20 (10): 2453-2463.
- Fellows, L.K., Farah, M.J. Dissociable elements of human foresight: a role for the ventromedial frontal lobes in framing the future, but not in discounting future rewards. *Neuropsychologia*, 2005. 43 (8): 1214-1221.

- Forbes, C.E., Grafman, J. The Role of the Human Prefrontal Cortex in Social Cognition and Moral Judgment. *Annu Rev Neurosci*, 2010. 33: 299-324.
- Gauthier, I., James, T.W., Curby, K.M., Tarr, M.J. The influence of conceptual knowledge on visual discrimination. *Cognitive Neuropsychology*, 2003. 20 (3-6): 507-523.
- Goel, V., Grafman, J., Tajik, J., Gana, S., Danto, D. A study of the performance of patients with frontal lobe lesions in a financial planning task. *Brain*, 1997. 120 (Pt 10): 1805-1822.
- Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M. Classification of primary progressive aphasia and its variants. *Neurology*, 2011. 76 (11): 1006-1014.
- Green, S., Ralph, M.A., Moll, J., Stamatakis, E.A., Grafman, J., Zahn, R. Selective functional integration between anterior temporal and distinct fronto-mesolimbic regions during guilt and indignation. *Neuroimage*, 2010. 52 (4): 1720-1726.
- Green, S., Ralph, M.A.L., Moll, J., Deakin, J.F.W., Zahn, R. Guilt-Selective Functional Disconnection of Anterior Temporal and Subgenual Cortices in Major Depressive Disorder. *Arch Gen Psychiatry*, 2012. 69 (10): 1014-1021.
- Grossman, M., Eslinger, P.J., Troiani, V., Anderson, C., Avants, B., Gee, J.C., McMillan, C., Massimo, L., Khan, A., Antani, S. The role of ventral medial prefrontal cortex in social decisions Converging evidence from fMRI and frontotemporal lobar degeneration. *Neuropsychologia*, 2010. 48 (12): 3505-3512.
- Hodges, J.R. Frontotemporal dementia (Pick's disease): clinical features and assessment. *Neurology*, 2001. 56 (11 Suppl 4): S6-10.
- Hoffman, P., Jones, R.W., Ralph, M.A. The degraded concept representation system in semantic dementia: damage to pan-modal hub, then visual spoke. *Brain*, 2012. 135 (Pt 12): 3770-3780.
- Howard, D., Patterson, K. *The Pyramids and Palm Trees Test*. Thames Valley Test Company: Flempton, 1992.
- Kedia, G., Berthoz, S., Wessa, M., Hilton, D., Martinot, J.L. An agent harms a victim: a functional magnetic resonance imaging study on specific moral emotions. *J Cogn Neurosci*, 2008. 20 (10): 1788-1798.
- Krueger, F., Moll, J., Zahn, R., Heinecke, A., Grafman, J. Event Frequency Modulates the Processing of Daily Life Activities in Human Medial Prefrontal Cortex. *Cereb Cortex*, 2007a. 17 (10): 2346-2353.
- Krueger, F., Rostami, E., Huey, E.D., Snyder, A., Grafman, J. Evidence of an inferior total-order planning strategy in patients with frontotemporal dementia. *Neurocase*, 2007b. 13 (5): 426-437.
- Krueger, F., Spampinato, M.V., Barbey, A.K., Huey, E.D., Morland, T., Grafman, J. The frontopolar cortex mediates event knowledge complexity: a parametric functional MRI study. *Neuroreport*, 2009. 20 (12): 1093-1097.
- Lambon Ralph, M.A., Patterson, K. Generalization and differentiation in semantic memory: insights from semantic dementia. *Annals of the New York Academy of Sciences*, 2008. 1124: 61-76.

- Liu, W., Miller, B.L., Kramer, J.H., Rankin, K., Wyss-Coray, C., Gearhart, R., Phengrasamy, L., Weiner, M., Rosen, H.J. Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. *Neurology*, 2004. 62 (5): 742-748.
- McKhann, G.M., Albert, M.S., Grossman, M., Miller, B., Dickson, D., Trojanowski, J.Q. Clinical and pathological diagnosis of Frontotemporal Dementia - Report of the work group on Frontotemporal Dementia and Pick's disease. *Archives of Neurology*, 2001. 58 (11): 1803-1809.
- Mendez, M.F. The Unique Predisposition to Criminal Violations in Frontotemporal Dementia. *Journal of the American Academy of Psychiatry and the Law*, 2010. 38 (3): 318-323.
- Mendez, M.F., Anderson, E., Shapira, J.S. An investigation of moral judgement in frontotemporal dementia. *Cognitive and Behavioral Neurology*, 2005a. 18 (4): 193-197.
- Mendez, M.F., Chen, A.K., Shapira, J.S., Miller, B.L. Acquired sociopathy and frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders*, 2005b. 20 (2-3): 99-104.
- Mendez, M.F., Shapira, J.S. Altered emotional morality in frontotemporal dementia. *Cogn Neuropsychiatry*, 2009. 14 (3): 165-179.
- Miller, B.L., Cummings, J.L., Villanuevameyer, J., Boone, K., Mehninger, C.M., Lesser, I.M., Mena, I. FRONTAL-LOBE DEGENERATION - CLINICAL, NEUROPSYCHOLOGICAL, AND SPECT CHARACTERISTICS. *Neurology*, 1991. 41 (9): 1374-1382.
- Miller, B.L., Darby, A., Benson, D.F., Cummings, J.L., Miller, M.H. Aggressive, socially disruptive and antisocial behaviour associated with fronto-temporal dementia. *British Journal of Psychiatry*, 1997. 170: 150-155.
- Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., Hodges, J.R. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 2006. 21 (11): 1078-1085.
- Moll, J., de Oliveira-Souza, R., Garrido, G.G., Bramati, I.E., Caparelli-Daquer, E.M.A., Paiva, M.L.M.F., Zahn, R., Grafman, J. The self as a moral agent: linking the neural bases of social agency and moral sensitivity. *Social Neuroscience*, 2007. 2: 336-352.
- Moll, J., Zahn, R., de Oliveira-Souza, R., Bramati, I.E., Krueger, F., Tura, B., Cavanagh, A.L., Grafman, J. Impairment of prosocial sentiments is associated with frontopolar and septal damage in frontotemporal dementia. *Neuroimage*, 2011. 54 (2): 1735-1742.
- Moll, J., Zahn, R., de Oliveira-Souza, R., Krueger, F., Grafman, J. The neural basis of human moral cognition. *Nat Rev Neurosci*, 2005. 6 (10): 799-809.
- Morey, R.A., McCarthy, G., Selgrade, E.S., Seth, S., Nasser, J.D., LaBar, K.S. Neural systems for guilt from actions affecting self versus others. *NeuroImage*, 2012. 60 (1): 683-692.
- Mummery, C.J., Patterson, K., Price, C.J., Ashburner, J., Frackowiak, R.S.J., Hodges, J.R. A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. *Annals of Neurology*, 2000. 47 (1): 36-45.
- Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, 1998. 51 (6): 1546-1554.

- Neary, D., Snowden, J.S., Mann, D.M.A. THE CLINICAL-PATHOLOGICAL CORRELATES OF LOBAR ATROPHY. *Dementia*, 1993. 4 (3-4): 154-159.
- Patterson, K., Nestor, P.J., Rogers, T.T. Where do you know what you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience*, 2007. 8 (12): 976-987.
- Pobric, G., Lambon Ralph, M.A., Zahn, R. Hemispheric Specialization within the Superior Anterior Temporal Cortex for Social and Nonsocial Concepts. *J Cogn Neurosci*, 2016. 28 (3): 351-360.
- Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., van Swieten, J.C., Seelaar, H., Dopper, E.G.P., Onyike, C.U., Hillis, A.E., Josephs, K.A., Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.L., Rosen, H., Prioleau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C., Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M., Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M., Miller, B.L. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, 2011. 134: 2456-2477.
- Rice, G.E., Hoffman, P., Lambon Ralph, M.A. Graded specialization within and between the anterior temporal lobes. *Annals of the New York Academy of Sciences*, 2015a. 1359: 84-97.
- Rice, G.E., Lambon Ralph, M.A., Hoffman, P. The Roles of Left Versus Right Anterior Temporal Lobes in Conceptual Knowledge: An ALE Meta-analysis of 97 Functional Neuroimaging Studies. *Cereb Cortex*, 2015b. 25 (11): 4374-4391.
- Rosen, H.J., Perry, R.J., Murphy, J., Kramer, J.H., Mychack, P., Schuff, N., Weiner, M., Levenson, R.W., Miller, B.L. Emotion comprehension in the temporal variant of frontotemporal dementia. *Brain*, 2002. 125: 2286-2295.
- Ross, L.A., Olson, I.R. Social cognition and the anterior temporal lobes. *NeuroImage*, 2010. 49 (4): 3452-3462.
- Salmon, E., Garraux, G., Delbeuck, X., Collette, F., Kalbe, E., Zuendorf, G., Perani, D., Fazio, F., Herholz, K. Predominant ventromedial frontopolar metabolic impairment in frontotemporal dementia. *Neuroimage*, 2003. 20 (1): 435-440.
- Saver, J.L., Damasio, A.R. Preserved Access and Processing of Social Knowledge in a Patient with Acquired Sociopathy Due to Ventromedial Frontal Damage. *Neuropsychologia*, 1991. 29 (12): 1241-1249.
- Shallice, T. *From Neuropsychology to Mental Structure*. Cambridge University Press: Cambridge, 1990.
- Simmons, W.K., Reddish, M., Bellgowan, P.S.F., Martin, A. The Selectivity and Functional Connectivity of the Anterior Temporal Lobes. *Cereb. Cortex*, 2009: bhp149.
- Sirigu, A., Zalla, T., Pillon, B., Grafman, J., Agid, Y., Dubois, B. Encoding of sequence and boundaries of scripts following prefrontal lesions. *Cortex*, 1996. 32 (2): 297-310.
- Skipper, L.M., Ross, L.A., Olson, I.R. Sensory and semantic category subdivisions within the anterior temporal lobes. *Neuropsychologia*, 2011. 49 (12): 3419-3429.

- Snowden, J.S., Bathgate, D., Varma, A., Blackshaw, A., Gibbons, Z.C., Neary, D. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Ps*, 2001. 70 (3): 323-332.
- Snowden, J.S., Thompson, J.C., Stopford, C.L., Richardson, A.M.T., Gerhard, A., Neary, D., Mann, D.M.A. The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships. *Brain*, 2011. 134: 2478-2492.
- Sollberger, M., Stanley, C.M., Wilson, S.M., Gyurak, A., Beckman, V., Growdon, M., Jang, J., Weiner, M.W., Miller, B.L., Rankin, K.P. Neural basis of interpersonal traits in neurodegenerative diseases. *Neuropsychologia*, 2009. 47 (13): 2812-2827.
- Takahashi, H., Yahata, N., Koeda, M., Matsuda, T., Asai, K., Okubo, Y. Brain activation associated with evaluative processes of guilt and embarrassment: an fMRI study. *Neuroimage*, 2004. 23 (3): 967-974.
- Wood, J.N., Grafman, J. Human prefrontal cortex: Processing and representational perspectives. *Nature Reviews Neuroscience*, 2003. 4 (2): 139-147.
- Wood, J.N., Knutson, K.M., Grafman, J. Psychological structure and neural correlates of event knowledge. *Cereb Cortex*, 2005a. 15 (8): 1155-1161.
- Wood, J.N., Tierney, M., Bidwell, L.A., Grafman, J. Neural correlates of script event knowledge: a neuropsychological study following prefrontal injury. *Cortex*, 2005b. 41 (6): 796-804.
- Zahn, R., de Oliveira-Souza, R., Moll, J. The neuroscience of moral cognition and emotion. *The Oxford handbook of social neuroscience*. Oxford University Press, 2011. pp. 477-490.
- Zahn, R., de Oliveira-Souza, R., Moll, J. The Neural Foundation of Morality. in: Wright, J.D. (Ed.), *International Encyclopedia of Social and Behavioral Science*, . Elsevier, 2015.
- Zahn, R., Moll, J., Garrido, G., Krueger, F., Huey, E.D., Grafman, J. Social concepts are represented in the superior anterior temporal cortex. *Proceedings of the National Academy of Sciences (USA)*, 2007. 104: 6430 - 6435.
- Zahn, R., Moll, J., Iyengar, V., Huey, E.D., Tierney, M., Krueger, F., Grafman, J. Social conceptual impairments in frontotemporal lobar degeneration with right anterior temporal hypometabolism. *Brain*, 2009a. 132 (Pt 3): 604-616.
- Zahn, R., Moll, J., Paiva, M., Garrido, G., Krueger, F., Huey, E.D., Grafman, J. The Neural Basis of Human Social Values: Evidence from Functional MRI. *Cereb Cortex*, 2009b. 19 (2): 276-283.
- Zamboni, G., Huey, E.D., Krueger, F., Nichelli, P.F., Grafman, J. Apathy and disinhibition in frontotemporal dementia - Insights into their neural correlates. *Neurology*, 2008. 71 (10): 736-742.

Table 1 Group comparisons on core neuropsychological tests

	Control mean±standard deviation	Control n	FTLD mean±standard deviation	FTLD n	p-value	FTLD ratio number of cases impaired / total
Addenbrooke's Cognitive Examination-Revised score	96.5±3.2	19	63.9±15.35	19	<.0001*	18/19
Cambridge Semantic Test Battery – Naming (64 items) [number correct]	63.5±.61	19	40.3±17.21	17	<.0001*	17/17
Cambridge Semantic Test Battery – Word to Picture Matching (64 items) [number correct]	63.6±0.60	19	49.8±13.34	18	<.0001*	18/18
Visual Discrimination [% correct]	90.6±6.77	19	92.8±7.05	19	=.335 ^{n.s.}	1/19
Animal Function Concept Discrimination [% correct]	93.6±5.07	19	80.9±12.98	19	.001*	12/19
Social Concept Discrimination [% correct]	89.8±4.03	19	65.7±14.51	19	<.0001*	16/19
Short-term Consequences Discrimination [% correct]	97.4±3.61	19	90.3±8.75	19	=.004*	10/19
Long-term Consequences Discrimination [% correct]	87.2±3.89	19	75.4±11.82	19	<.0001*	9/19

The number of patients with impairments (< healthy control mean – 2 standard deviations). Naming and Word-to-Picture Naming Tasks were taken from the Cambridge Semantic Test Battery (64 items). * marks significance at 2-tailed $p<.05$. n.s. marks non-significance at 2-tailed $p=.05$.

Figure Legends

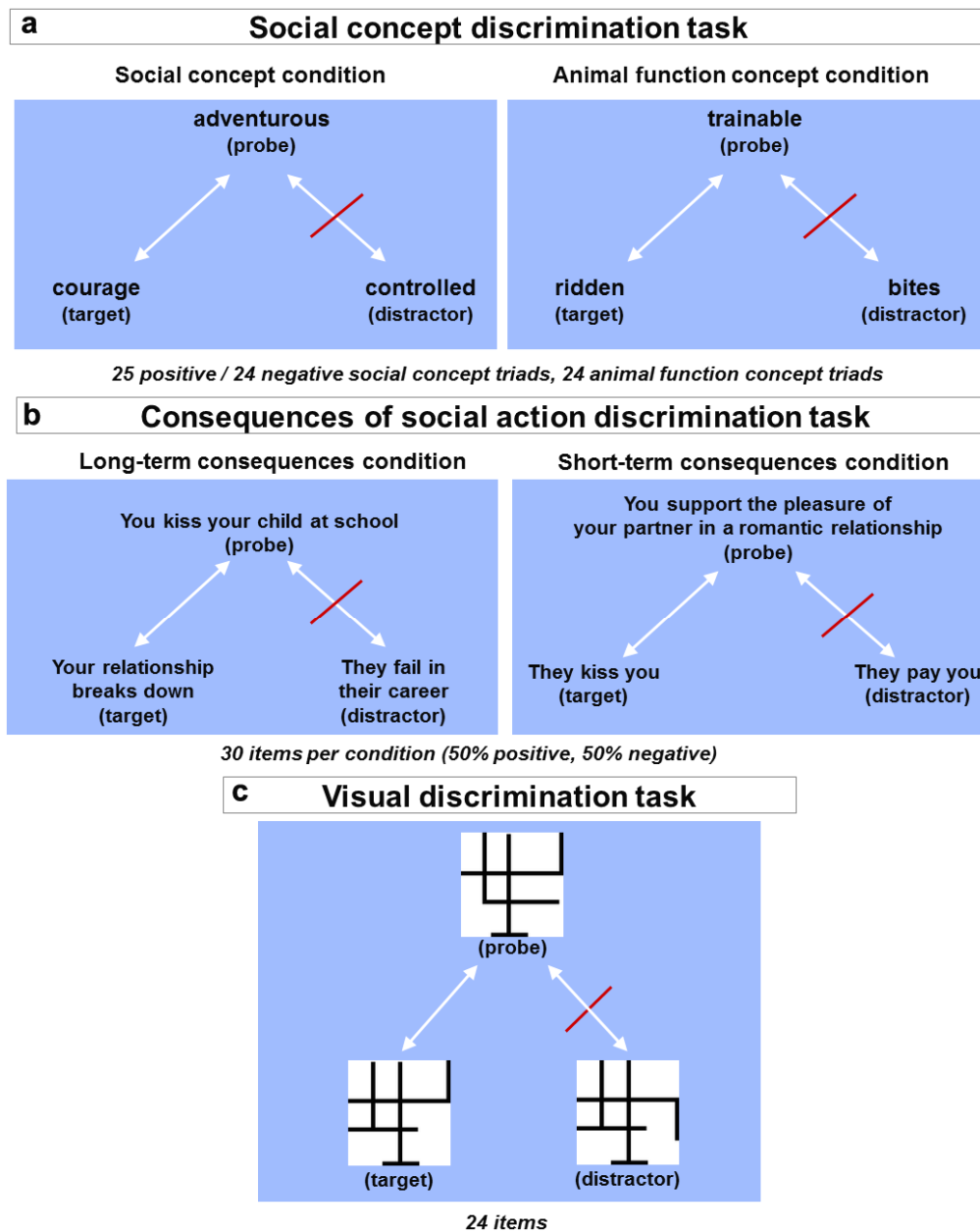


Figure 1. Overall design of a| Social Concept Discrimination Task (Zahn et al., 2009), b| Consequences of Social Action Discrimination Task, c| Visual Discrimination Task

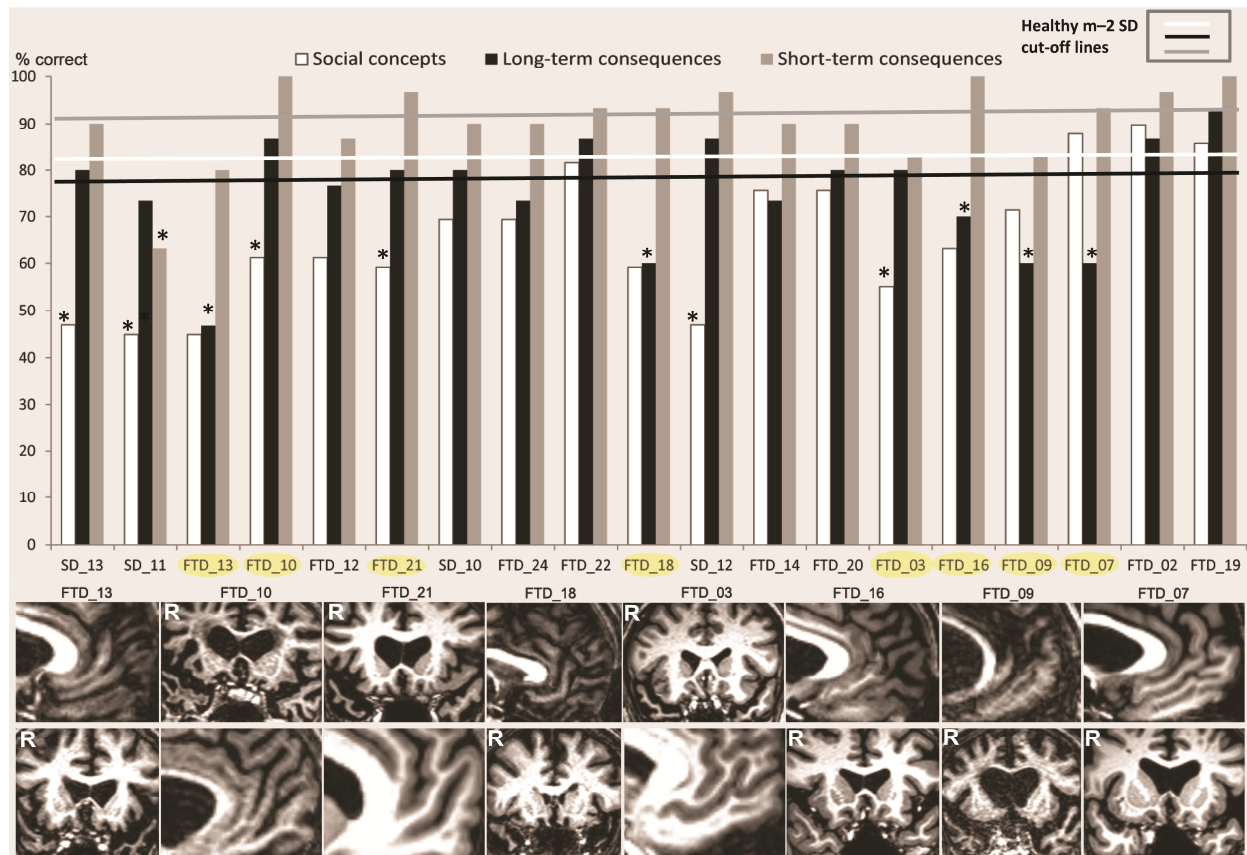


Figure 2

Performance on the Social Concept (white), Long-term Consequences (black), and Short-term Consequences (grey) task conditions are displayed for each patient (% correct). Patients are ordered according to their Addenbrooke's Cognitive Examination-R scores (left for lowest to right for highest scores). White, black, and grey lines represent healthy control means – 2 standard deviation cut-off values for each task. Using a well-established method (Crawford and Garthwaite, 2005), significant dissociations at $p < .0026$ (corresponding to an approximate Bonferroni-corrected $p < .05$ across 19 single patient cases) for Long-term vs. Short-term Consequences and Social Concept vs. Long-term Consequences conditions were marked with an asterisk. There was one patient with a selective impairment on Long-term Consequences vs. Social Concepts (FTD_7). Another patient displayed a selective impairment on Short-term vs. Long-term Consequences

(SD_11). The upper row of T1-weighted MRI scans displays coronal sections through the anterior temporal lobes for 3 patients showing a Social Concept-selective impairment relative to Long-term Consequences (FTD_10, FTD_21, FTD_3), no MRI scans were available for additional 3 patients showing this dissociation (SD_13, SD_11, SD_12). The upper row also shows mid-sagittal slices through the frontopolar and ventromedial frontal cortices of all the 5 patients exhibiting a selective impairment for Long-term vs. Short-term Consequences (FTD_13, FTD_18, FTD_16, FTD_09, FTD_07). The lower row displays slices to depict the 2nd region of interest for comparison (frontopolar for patients with Social Concept-selective and anterior temporal for patients with Long-term Consequences-selective impairments).

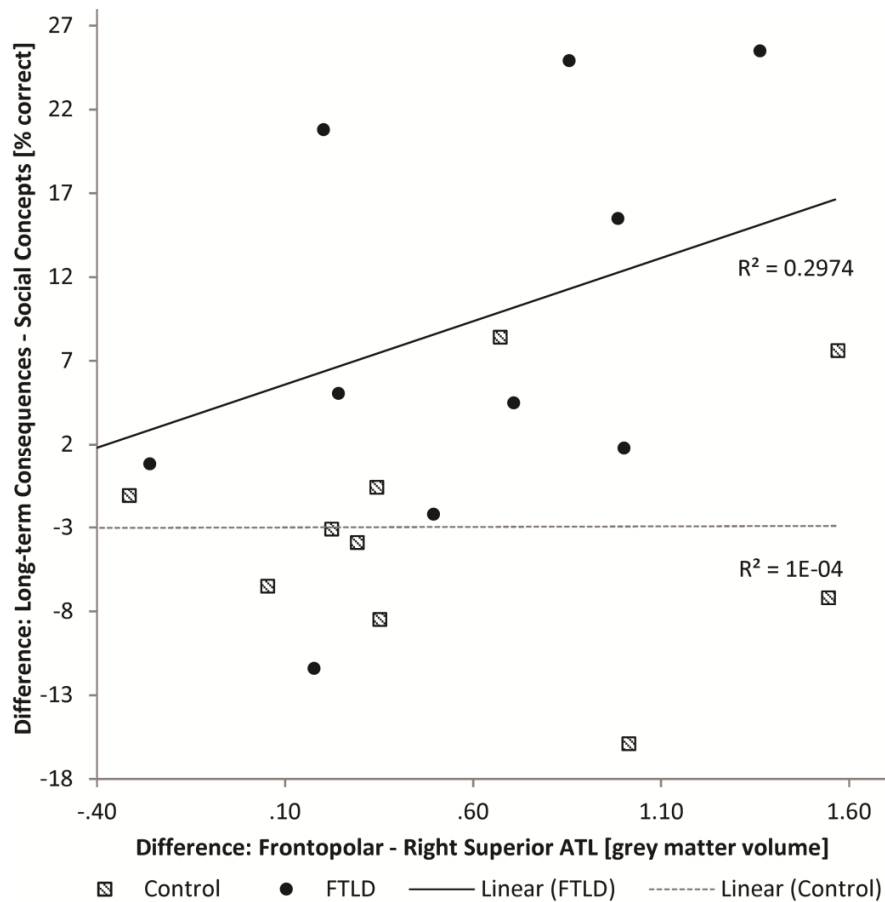


Figure 3

Difference scores for performance on the Long-term Consequences vs. Social Concept task conditions [% correct] were plotted against difference scores in frontopolar cortex (i.e. BA10) vs. right superior ATL grey matter volumes in n=15 FTL patients and n=15 healthy control participants. There was a positive association between both difference scores in the FTL group such that lower frontopolar relative to ATL volume was associated with poorer performance on Long-term Consequences relative to Social Concepts and vice versa. The control group showed no such relationship between neuropsychological and brain region difference scores.

Supplementary Materials

Frontotemporal lobar degeneration and social behaviour: dissociation between the knowledge of its consequences and its conceptual meaning

Roland Zahn^{1,2,*}, Sophie Green², Helen Beaumont^{2,3}, Alistair Burns⁴, Jorge Moll⁵, Diana Caine^{2,6}, Alexander Gerhard⁴, Paul Hoffman², Benjamin Shaw⁴, Jordan Grafman⁷, Matthew A. Lambon Ralph²

¹ *Institute of Psychiatry, Psychology & Neuroscience, Department of Psychological Medicine, King's College London, London, SE5 8AZ, UK*

² *Neuroscience and Aphasia Research Unit, Division of Neuroscience and Experimental Psychology, The University of Manchester, Manchester, UK*

³ *Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA*

⁴ *Division of Neuroscience and Experimental Psychology, The University of Manchester, Manchester, UK*

⁵ *Cognitive and Behavioral Neuroscience Unit, LABS-D'Or Hospital Network, Rio de Janeiro, RJ, Brazil*

⁶ *National Hospital for Neurology & Neurosurgery, Queen Square, London, UK.*

⁷ *Rehabilitation Institute of Chicago, Chicago, Illinois & Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, Illinois, USA*

** To whom correspondence should be addressed:*

Dr. Roland Zahn (see address above)

E-mail: roland.zahn@kcl.ac.uk

Phone: 0044-(0)20 7848 0348

Fax: 0044-(0)20 7848 0298

Supplementary Methods

Consequences of Social Action Task Design

We created probe items which were descriptions of social behaviours, and target/distracter items which described consequences of social behaviours, using normative data from two pre-studies. Social behaviours included a specific agent and recipient and the overall context was specified (particular situation). Target/distracter items were either short- or long-term consequences.

1.1.1 Social behaviour probe generation

The first normative study using the “Social Scenario Generation Task” was carried out at the National Institutes of Health, Bethesda, USA and has been described elsewhere (Green et al., 2013). In brief, participants were asked to provide social behaviours that are examples of social concepts (e.g. an example of a behaviour that is “stingy”, or “tactless”). Two independent raters obtained good inter-rater agreement for categorizing the responses into categories for recipient role, primary social action, and sequential context in order to group similar social behaviours together. These categories were then synthetically recombined to create the social behaviour probes for the development of our novel task here.

We identified the two or three most frequently co-occurring categories for recipient role (e.g. “friend”), primary social action (e.g. “helping”) and sequential context (e.g. “at work”, “at school”) in order to create social behaviours that occurred between two people in particular situations. The category labels for the primary social action derived from the pre-studies were used without changes (e.g., “helping”, “giving a gift”, “ignoring requests”) as the social behaviour probes. The only exception was for the category of ‘inferior role’ for

recipient/agent roles (e.g. an “amateur musician” is inferior to a “professional musician” when “playing a piece at a recital”); in this case another recipient was used.

Highly related categories were collapsed for stimulus creation (e.g. “verbally attacking”/”criticizing”/”accusing”), and the most relevant or appropriate term was used for each social behaviour probe, given the recipient role and the sequential context, in order to create variation between the stimuli. The median pleasantness and unpleasantness of the stimuli were determined to create social behaviour probes that were either positive or negative by aggregating the median of rated pleasantness and unpleasantness over the co-occurring primary social action, recipient role and sequential context categories. The created social behaviour descriptions were then presented as probe stimuli in the second normative study that was used to generate data about the anticipated consequences of social knowledge.

1.1.2 Consequences of Social Action Task Normative Study

The task was comprised of 15 pleasant social behaviour probes and 15 unpleasant social behaviour probes. The order of presentation of positive vs. negative stimuli was randomized across participants. They were entered into Excel Microsoft Visual Basic Editor and presented to 22 healthy participants (15 female, age: 24.0 ± 8.4 years, education: 17.3 ± 3.4 years) who gave written informed consent at the School of Psychological Sciences at the University of Manchester, where research ethics approval had been obtained. Participants were first required to complete a free association task using the social behaviour probes. Participants had to write down the first thing that enters their mind when reading the description of social behaviour.

Participants then completed the short-term consequences task (Supplementary Figures 1 and 2). They gave a detailed example of the general behaviour described in the

stimulus, and then provided a short-term, immediate consequence of this specific behaviour, rated the pleasantness/unpleasantness of the short-term consequences (-4/+4 bipolar scale) as well as the probability of this as a consequence of the social behaviour described in the probe sentence (an estimate between 0 – 100 %) and how familiar they are with the consequence (1=not at all familiar – 7= very familiar).

They then completed the long-term consequences task, providing a chain of events that occurred in sequence following from the short-term consequence and resulting in a long-term, ultimate consequence. The long-term consequence had to be at least 5 years into the future. They then rated the pleasantness/unpleasantness of the long-term consequences as well as the probability of the consequences occurring and how familiar they are with them (all measures on the same scales as for the short-term consequence).

1.2.3 Creating consequence categories (targets and distracters)

We categorized participants' responses based on features of the consequence generated using categories which were similar enough so that very different behaviours were kept separate but broad enough so that similar consequences could be grouped. This was done for both short-term and long-term consequences. Categories were created for the primary social action (e.g. in the short-term consequence condition: "violently attacks", "verbally attacks", "punishes", "thanks", "rejects", "gets found out", "donates possessions"; in the long-term consequence condition: "develops health problems", "gets into trouble with the law/sent to prison", "succeeding in their career", "failing in their career", "has children"), for the agent and recipient role of the behaviour (e.g. "child - parent", "spouse", "employer-employee"), and who it is that the consequences would affect (self, other).

1.2.4 Categorization of consequence data from normative study

Occasionally data had to be recoded for participants who had not entered the consequence into the correct pre-defined field. On rare occasions for the long-term consequences, responses were too abstract or broad to be concretely defined as a consequence (e.g. “live a happy life”) and so the consequence provided before as one of the ‘steps’ leading to the long-term consequence were taken, or the ‘gist’ of the statement had to be inferred from previous information provided by the rest of the data for that item from that participant. Occasionally, participants had not provided a long-term consequence that was far enough into the future, and instead had replicated the short-term consequence that they had provided. In this case, their long-term consequence result was not used. Sometimes, the ultimate long-term consequence that was provided was of a different valence to the rest of the ‘steps’ provided by the participant, and in such cases the consequence step before this was used. In cases where participants provided a chain of consequences that were completely of the opposite valence to the probe, their data were excluded for that item.

1.2.5 Construction of stimuli for the final patient task

The probe labels were used as derived from the pre-studies, however the agent roles of the social behaviour were transformed into “You”, with stimuli presented as e.g., “You kiss your colleague at work”. A number of criteria were generated and followed when producing the stimuli:

- 1) The target consequence was chosen based on its frequency of its association with the probe category in our normative data. In most cases, the most frequently associated category was selected as the target. In these cases, the distracter was a consequence category that either occurred once or not at all as associated with that particular social

behaviour probe. In a few cases, there was a variety of consequence categories associated with a given social behaviour probe. In these cases the target was associated with the probe at least twice, and the distracter had to be selected from responses generated to an unrelated social behaviour probe.

- 2) The target and distracter were produced so that they were equally conceptually related to the stimulus item. For example, take the probe “*You achieve at work*”, and consider the possible alternatives- the target could be “*You get a promotion*” and the distracter could be “*You develop health problems*”. Here, “*work*” is conceptually more related to “*promotion*” than “*health problems*”. Thus the distracter would not have been chosen because it would have allowed a correct response based on conceptual rather than sequential relationships. To make distracters more or equally related to the probes than targets, sometimes the distracter would be formulated by negating a previously positive social behaviour.
- 3) We did not introduce a third party into the stimuli, because this could have increased task demands for the FTLD group.
- 4) The distracter and target were not consequences of one another, for example the target “*You fail in your career*”, would not have been used following distracter “*Your standard of living decreases*”.
- 5) Care was taken, not to allow the target and distracter being examples of one another (i.e. a superordinate-subordinate relationship, e.g. “*You are rewarded*” and “*You are promoted*”).

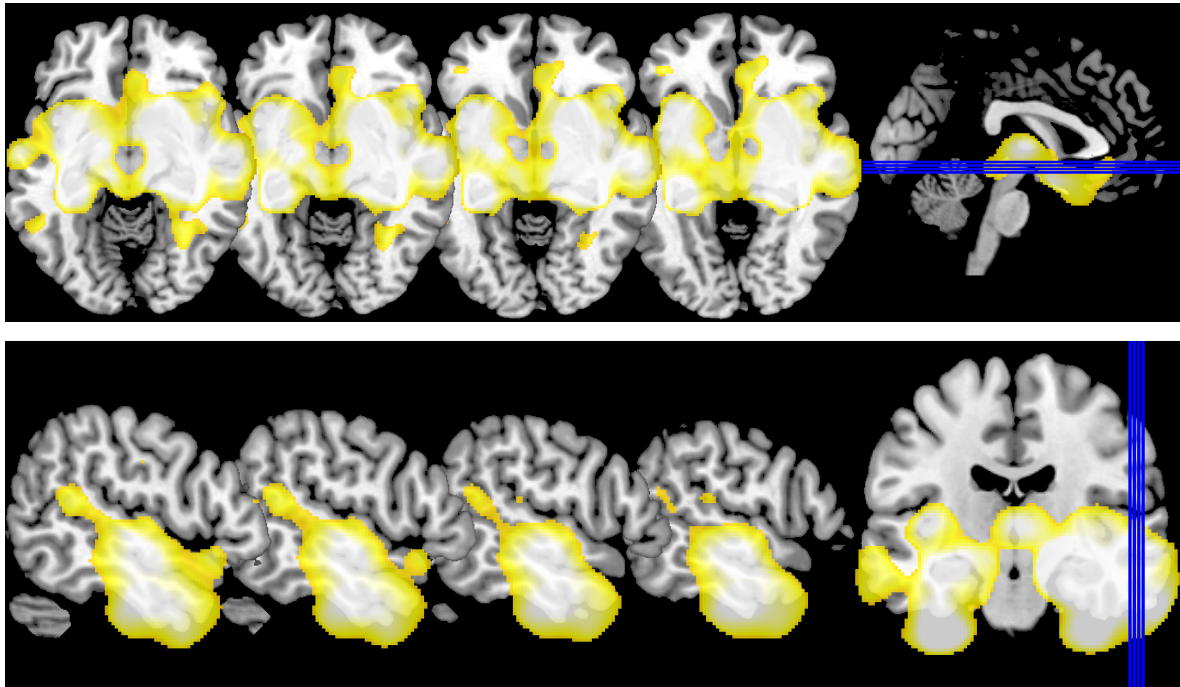
Supplementary Figures

Imagine that you...	kiss your colleague at work																				
Can you give a more specific example of this kind of behaviour ?	I like my colleague at work and think that she likes me too so I try to kiss her.																				
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 25%; padding: 5px;">What is the immediate</td> <td colspan="3" style="padding: 5px;">unpleasant consequence of this behaviour ?</td> </tr> <tr> <td style="padding: 5px;">Who acts (agent) ?</td> <td style="padding: 5px;">Properties of agent ?</td> <td style="padding: 5px;">Towards Whom (recipient) ?</td> <td style="padding: 5px;">Properties of recipient ?</td> </tr> <tr> <td style="padding: 5px;">my colleague</td> <td style="padding: 5px;">none</td> <td style="padding: 5px;">me</td> <td style="padding: 5px;">attracted to her</td> </tr> <tr> <td style="padding: 5px;">Did what (action) ?</td> <td style="padding: 5px;">Properties of action ?</td> <td style="padding: 5px;">In what situation ?</td> <td style="padding: 5px;">Properties of situation ?</td> </tr> <tr> <td style="padding: 5px;">rejected me</td> <td style="padding: 5px;">immediately</td> <td style="padding: 5px;">work</td> <td style="padding: 5px;">none</td> </tr> </table>		What is the immediate	unpleasant consequence of this behaviour ?			Who acts (agent) ?	Properties of agent ?	Towards Whom (recipient) ?	Properties of recipient ?	my colleague	none	me	attracted to her	Did what (action) ?	Properties of action ?	In what situation ?	Properties of situation ?	rejected me	immediately	work	none
What is the immediate	unpleasant consequence of this behaviour ?																				
Who acts (agent) ?	Properties of agent ?	Towards Whom (recipient) ?	Properties of recipient ?																		
my colleague	none	me	attracted to her																		
Did what (action) ?	Properties of action ?	In what situation ?	Properties of situation ?																		
rejected me	immediately	work	none																		
<table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">How unpleasant/pleasant do you find this consequence?</div> <div style="display: flex; align-items: center;"> <div style="flex: 1; text-align: center;"> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> -4-3-2-101234 </div> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> extremely unpleasantneutralextremely pleasant </div> </div> </div></td> <td style="width: 50%; vertical-align: top;"> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">How familiar are you with this consequence?</div> <div style="display: flex; align-items: center;"> <div style="flex: 1; text-align: center;"> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> 1234567 </div> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> Not at all familiarNeutralVery familiar </div> </div> </div> </td> </tr> </table>		<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">How unpleasant/pleasant do you find this consequence?</div> <div style="display: flex; align-items: center;"> <div style="flex: 1; text-align: center;"> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> -4-3-2-101234 </div> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> extremely unpleasantneutralextremely pleasant </div> </div> </div>	<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">How familiar are you with this consequence?</div> <div style="display: flex; align-items: center;"> <div style="flex: 1; text-align: center;"> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> 1234567 </div> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> Not at all familiarNeutralVery familiar </div> </div> </div>																		
<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">How unpleasant/pleasant do you find this consequence?</div> <div style="display: flex; align-items: center;"> <div style="flex: 1; text-align: center;"> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> -4-3-2-101234 </div> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> extremely unpleasantneutralextremely pleasant </div> </div> </div>	<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">How familiar are you with this consequence?</div> <div style="display: flex; align-items: center;"> <div style="flex: 1; text-align: center;"> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> 1234567 </div> <div style="display: flex; justify-content: space-between; padding: 0 10px;"> Not at all familiarNeutralVery familiar </div> </div> </div>																				
<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;">How likely is it that this consequence would occur in response to the social behaviour? (0 - 100%)</div> <div style="display: flex; justify-content: space-between; align-items: center;"> <div style="border: 1px solid black; padding: 2px; background-color: yellow;">90%</div> <div style="border: 1px solid black; padding: 5px 15px;">Continue</div> </div>																					

Supplementary Figure 1. Short-term consequences task pre-study. Participants completed the fields to provide a dataset of consequences which are perceived to occur after particular social behaviours to enable construction of short- and long-term consequence target and distracters for the *Consequences of Social Action Task*.

Imagine that you	kiss your colleague at work			
Immediate consequence you gave: agent, properties / action, properties / recipient, properties / situation, properties				
my colleague, none/ rejects me, immediately/ me, attracted to her/ work, none				
What happens next? (Step 1)	I am embarrassed so quit my job.			
Then what, if anything? (Step 2)	I like other people in the future but do not show them as they may reject me.			
Then what, if anything? (Step 3)	I never get romantically involved again.			
Then what, if anything? (Step 4)	I die alone.			
What is the ultimate	unpleasant consequence of this behaviour ?			
Who acts (agent) ?	Properties of agent ?	Towards Whom (recipient) ?	Properties of recipient ?	
no one	none	me	dead and buried	
Did what (action) ?	Properties of action ?	In what situation ?	Properties of situation ?	
leaves flowers on my grave	none	cemetery	none	
How unpleasant/pleasant do you find this consequence?		How familiar are you with this consequence?		
<div style="display: flex; align-items: center;"> <div style="flex: 1; text-align: center;"> <div style="display: flex; justify-content: space-between; border-top: 1px solid black; border-bottom: 1px solid black; padding: 2px 0;"> ◀ -4 -3 -2 -1 0 1 2 3 4 ▶ </div> <div style="display: flex; justify-content: space-between; padding: 2px 0;"> extremely unpleasant neutral extremely pleasant </div> </div> <div style="flex: 1; text-align: center;"> <div style="display: flex; justify-content: space-between; border-top: 1px solid black; border-bottom: 1px solid black; padding: 2px 0;"> ◀ 1 2 3 4 5 6 7 ▶ </div> <div style="display: flex; justify-content: space-between; padding: 2px 0;"> Not at all familiar Neutral Very familiar </div> </div> </div>				
How likely is it that this consequence could occur in response to the social behaviour? (0 - 100%)				
<div style="display: flex; align-items: center;"> <div style="flex: 1; border: 1px solid black; position: relative;"> <div style="position: absolute; left: 0; top: 0; bottom: 0; width: 10%; background-color: yellow;"></div> <div style="position: absolute; left: 10%; top: 0; bottom: 0; width: 90%;"></div> </div> <div style="margin-left: 5px;">10%</div> </div>				
				Continue

Supplementary Figure 2. Long-term consequences task pre-study, required for generation of consequence target and distracters for *Consequences of Social Action Task*.



Supplementary Figure 3. Grey matter volume loss in our FTL D group with available research MRI scans overall (n=15) compared with elderly healthy control participants (n=15) with age as a covariate of no interest (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/>, random effects model, 2-sample t-test). The upper panel displays axial slices in the subcallosal area and the lower panel sagittal slices through the right anterior temporal lobe using MRICron (<http://people.cas.sc.edu/rorden/mricron/install.html> (Rorden and Brett, 2000)). Display threshold: uncorrected $p = .001$, 0 voxels. Regions surviving voxel-based familywise error correction at $p=.05$ were reported in Supplementary Table 4.

Supplementary Table 1

Target consequence Rating	Short-term consequences <i>mean ± standard deviation</i>	Long-term consequences <i>mean ± standard deviation</i>	p-value (2-sided)
Pleasantness (-4 to +4)	-0.06±2.88	-0.07±3.39	.986
Familiarity (1-7)	4.23±1.03	3.10±1.21	<.0001*
Likelihood (0-100)	67.09±10.94	38.51±18.95	<.0001*

Normative data for means across 30 items in each condition of the consequences of social action task are reported. Significance at $p=.05$ 2-sided using 2-sample t-tests are marked with *.

Supplementary Table 2

		Long-term	Short-term	Social	Cambridge	Cambridge
		consequences	consequences	concepts	Naming	Word to Picture
						Matching
Long-term consequences	rho	1.0	.52*	.21	.12	.10
	p		.02	.39	.66	.69
	n	19	19	19	17	18
Short-term consequences	rho	.52*	1.0	.38	.52*	.67**
	p	.02		.11	.03	.002
	n	19	19	19	17	18
Social concepts	rho	.21	.38	1.0	.60*	.74**
	p	.39	.11		.01	<.0001
	n	19	19	19	17	18
Cambridge Naming	rho	.12	.52*	.60*	1.0	.95**
	p	.66	.03	.01		<.0001
	n	17	17	17	17	17
Cambridge Word to Picture Matching	rho	0.10	.67**	.74**	.95**	1.0
	p	.69	.002	<.0001	<.0001	
	n	18	18	18	17	18

Spearman rho correlations between standard general semantic (Bozeat et al., 2000) and experimental task measures in FTLN patients. All p-values are two-tailed. Spearman rho correlations significant at the p=.05 level are marked with *. ** corresponds to significance at the p=.01 level.

Supplementary Table 3

		Long-term	Short-term	Social	ACE-R	ACE-R	ACE-R
		consequences	consequences	concepts	Total	Verbal	Visuo-spatial
Long-term consequences	rho	1.00	.52*	.21	.08	.11	-.03
	p		.02	.39	.74	.64	.89
Short-term consequences	rho	.52*	1.00	.38	.37	.41	-.14
	p	.02		.11	.12	.08	.58
Social concepts	rho	.21	.38	1.00	.72**	.71**	.15
	p	.39	.11		.0006	.0007	.54
ACE-R Total	rho	.08	.37	.72**	1.00	.99**	.29
	p	.74	.12	.0006		<.0001	.22
ACE-R Verbal	rho	.11	.41	.71**	.99**	1.00	.22
	p	.64	.08	.0007	<.0001		.37
ACE-R Visuo-spatial	rho	-.03	-.14	.15	.29	.22	1.00
	p	.89	.58	.54	.22	.37	

Spearman rho correlations between Total Addenbrooke's Cognitive Examination(ACE)-R scores (Mioshi et al., 2006), the sum of its verbal subtests (i.e. all subtests requiring the understanding and working with verbal materials), its visuo-spatial subtest, and experimental task measures in FTLN patients. All p-values are two-tailed. Spearman rho correlations significant at the p=.05 level are marked with *. ** corresponds to significance at the p=.01 level.

Supplementary Table 4

Patient ID	Clinical Diagnosis	Classification
FTD_10	bvFTD w. SD features	Global Mixed
FTD_24	bvFTD w. SD features	Global Mixed
FTD_03	bvFTD w. features of SD+	Primary ATL
FTD_12	SD	Primary ATL
FTD_13	SD	Primary ATL
FTD_14	SD	Primary ATL
FTD_18	SD w. bvFTD features	Primary ATL
FTD_20	SD w. bvFTD features	Primary ATL
FTD_21	SD	Primary ATL
FTD_22	SD	Primary ATL
SD_10	SD	Primary ATL
SD_11	SD	Primary ATL
SD_12	SD	Primary ATL
SD_13	SD	Primary ATL
FTD_02	bvFTD	Primary non-ATL
FTD_07	Mixed PPA w. bvFTD features	Primary non-ATL
FTD_09	bvFTD	Primary non-ATL
FTD_16	bvFTD	Primary non-ATL
FTD_19	bvFTD	Primary non-ATL

Clinical diagnoses were lead symptom-based (i.e. based on the first and most prominent symptom according to caregiver history (Zahn and Burns, 2017)), this proved to best differentiate FTLT from Alzheimer's disease in a neuropathological study (Barber et al., 1995) and is in accordance with Lund Manchester diagnostic criteria (Neary et al., 1998). Based on their clinical lead symptom as reported by carers (primary behavioural: non-ATL) vs. primary comprehension/naming: ATL), background neuropsychological tests (central semantic impairment yes: ATL, no: no ATL) and neuroimaging features (ATL atrophy on MRI: yes or no, global atrophy: yes or no), we classified patients into those with primary neurodegeneration of the ATLs (primary ATL group, n=12), those with primary neurodegeneration outside the ATL (primary non-ATL group, n=5, presumably involving frontal cortices, although we know that MRI is not sensitive to early changes (Hodges, 2001)) and those with global impairment or atrophy (n=2). SD = semantic dementia, bvFTD = behavioural variant of frontotemporal dementia, PPA = primary progressive aphasia, ATL = anterior temporal lobe. As expected, non-ATL patients had lower frontopolar relative to ATL grey matter volume (n=5, -0.221 ± 0.088) compared to the ATL group (n=8, -0.099 ± 0.042 , $t=3.4$, $p=.006$, Mann-Whitney-U test: $p=.045$) and non-ATL patients also showed accordingly poorer performance on long-term consequences vs. social concept task conditions (n=5, -5.60 ± 14.65) compared with the ATL group (n=12, 15.26 ± 13.99 , $t=2.8$, $p=.014$, Mann-Whitney-U test: $p=.037$). ⁺FTD_03 would have been classified as SD on the basis of her neuropsychological profile and MRI showing right ATL atrophy, but according to caregiver history presented primarily with inappropriate social behaviour over several years before developing impairments in naming, comprehension and object recognition.

Supplementary Table 5

Hemi- sphere	Area	x	y	z	Brodmann Area	t - score
R	Anterior parahippocampal gyrus	23	3	-14	34	10.99
R	Midbrain	18	-23	-9	-	8.45
L	Hippocampus	-38	-33	-3	-	7.67
L	Amygdala	-23	0	-18	-	6.99
R	Caudate tail	35	-33	0	-	6.96
L	Anterior inferior temporal/fusiform gyrus	-36	-7	-39	20	6.57
R	Anterior inferior temporal/fusiform gyrus	39	-8	-36	20	6.30
L	Clastrum	-32	-1	7	-	6.19

Voxel-based morphometry analysis using a 2-sample t-test in SPM8 <http://www.fil.ion.ucl.ac.uk/spm/> to identify grey matter volume loss in the FTLD (n=15) vs. healthy elderly control group (n=15) whilst using age as a covariate of no interest. Only areas exceeding a voxel level threshold of $P=0.001$ uncorrected, 0 voxels and voxel-based familywise error-corrected $P=.05$ over the whole brain are reported (these were side maxima in one large cluster which was the only cluster surviving a familywise error corrected threshold of $p=.05$ over the whole brain). Montreal Neurological Institute coordinates were reported and transformed to Talairach coordinates (using Matthew Brett's formula, <http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml>) to derive anatomical labels using the Talairach atlas (Talairach and Tournoux, 1988).

Supplementary References

- Barber, R., Snowden, J.S., Craufurd, D. Frontotemporal Dementia and Alzheimers-Disease - Retrospective Differentiation Using Information from Informants. *J Neurol Neurosur Ps*, 1995. 59 (1): 61-70.
- Bozeat, S., Lambon Ralph, M.A., Patterson, K., Garrard, P., Hodges, J.R. Non-verbal semantic impairment in semantic dementia. *Neuropsychologia*, 2000. 38 (9): 1207-1215.
- Green, S., Lambon Ralph, M.A., Moll, J., Zakrzewski, J., Deakin, J.F., Grafman, J., Zahn, R. The neural basis of conceptual-emotional integration and its role in major depressive disorder. *Soc Neurosci*, 2013. 8 (5): 417-433.
- Hodges, J.R. Frontotemporal dementia (Pick's disease): clinical features and assessment. *Neurology*, 2001. 56 (11 Suppl 4): S6-10.
- Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., Hodges, J.R. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 2006. 21 (11): 1078-1085.
- Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, 1998. 51 (6): 1546-1554.
- Rorden, C., Brett, M. Stereotaxic display of brain lesions. *Behavioural Neurology*, 2000. 12: 191-200.
- Talairach, J., Tournoux, P. *Co-Planar Stereotaxic Atlas of the Human Brain*. Thieme Medical Publishers: New York, 1988.
- Zahn, R., Burns, A. Dementia disorders: an overview. in: Waldemar, G., Burns, A. (Eds.), *Alzheimer's Disease*. Oxford University Press: Oxford, 2017.
- Zahn, R., Moll, J., Iyengar, V., Huey, E.D., Tierney, M., Krueger, F., Grafman, J. Social conceptual impairments in frontotemporal lobar degeneration with right anterior temporal hypometabolism. *Brain*, 2009. 132 (Pt 3): 604-616.